FAMILIAL HYPERLIPOPROTEINEMIAS

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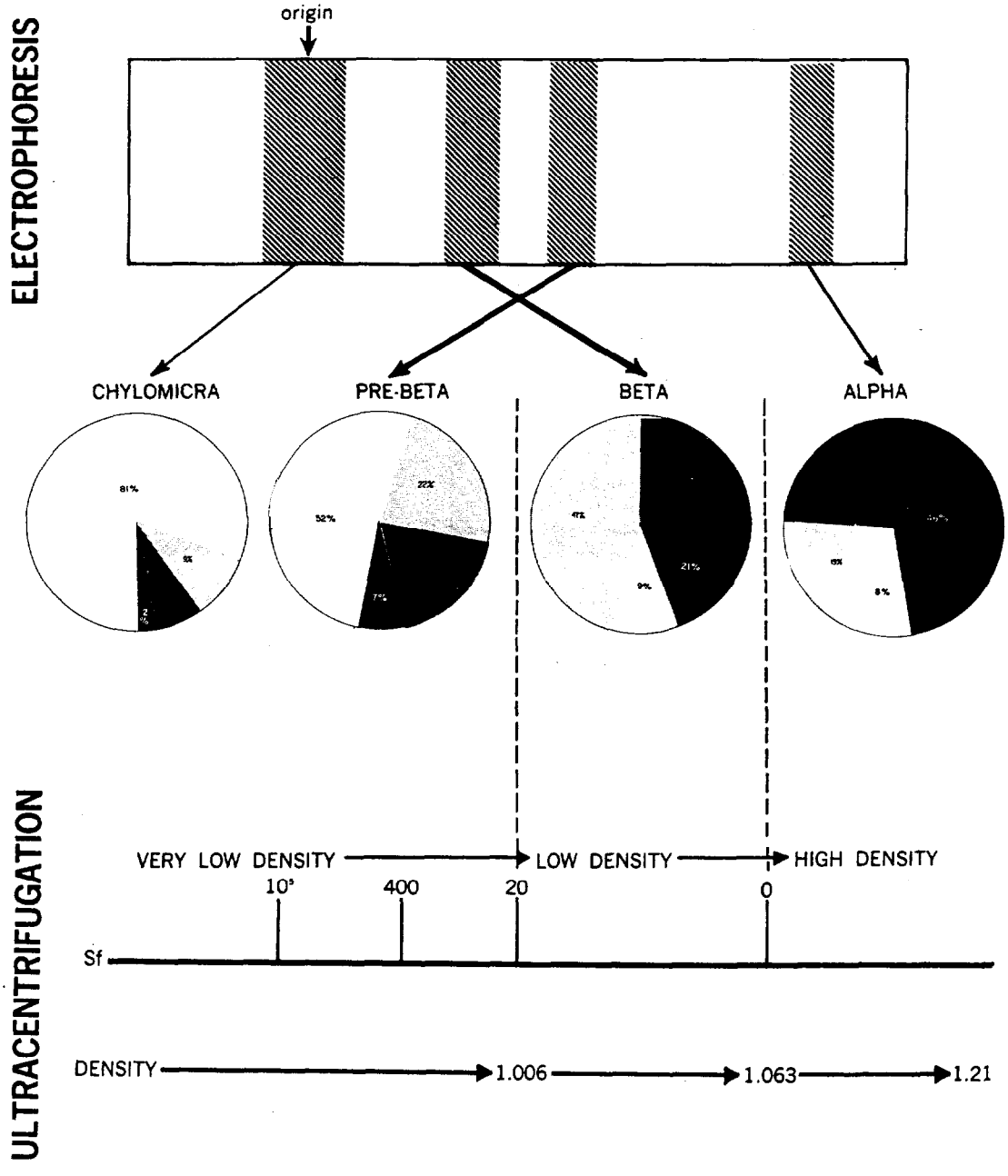
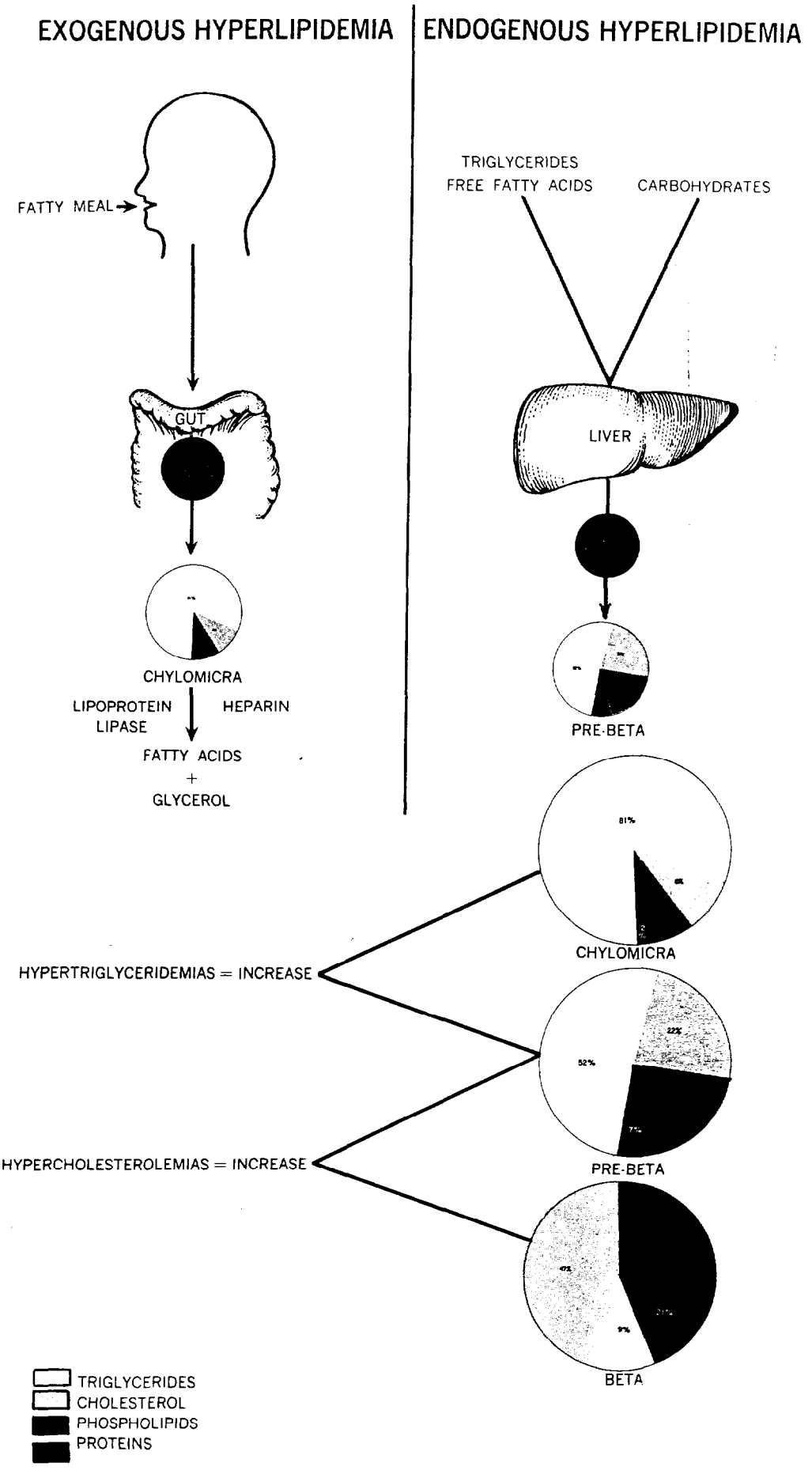
In 1929, Macheboeuf demonstrated that serum lipids do not circulate freely, but are bound to proteins in the form of large molecular complexes. Further investigations showed that these *lipoproteins* are composed of varying proportions of triglycerides, cholesterol, and phospholipids, bound to a protein. By means of analytic ultracentrifugation, it is possible to separate different types of lipoproteins since these molecules have different density, and thus migrate at varying measureable rates under a great centrifugal force. With this technique it is possible to separate the serum lipoproteins into four major groups: (a) chylomicra, (b) very low density lipoproteins, (c) low density lipoproteins, and (d) alpha lipoproteins[1]. It is also known that serum lipoproteins differ sufficiently, not only in density but also in electrostatic charges, to permit their separation by electrophoretic techniques. Fredrickson, Levy, and Lees[2], utilizing paper electrophoresis with barbital buffer, pH 8.6 containing 1 per cent albumin[3], were able to separate four distinct lipoprotein fractions, which were labelled as: chylomicra, beta, pre-beta, and alpha lipoproteins. These fractions correlate well with those separated by the ultracentrifuge. These lipoproteins have been isolated, and their lipid composition determined[4]. Based on the patterns of serum lipoproteins and serum lipid levels, Frederickson *et al.*[2] have been able to propose a new classification for familial hyperlipoproteinemias. The determination of serum lipoprotein patterns is not only a diagnostic tool, but it may also give significant information as to the pathophysiologic mechanism of a particular lipid metabolic derangement. The increase in chylomicra is usually associated with hyperlipidemias of exogenous origin; the pre-beta lipoproteins are synthesized in the liver from free fatty acids, triglycerides, and carbohydrates, and are the expression of an endogenous hyperlipidemia; beta lipoproteins are related to cholesterol metabolism, either of endogenous or exogenous origin.

PLASMA LIPOPROTEINS

Plasma triglycerides, cholesterol, and phospholipids do not circulate free, but they are bound to proteins to form complexes of high molecular weight known as lipoproteins. By means of electrophoresis or analytical ultracentrifugation, lipoproteins can be separated into four major groups.

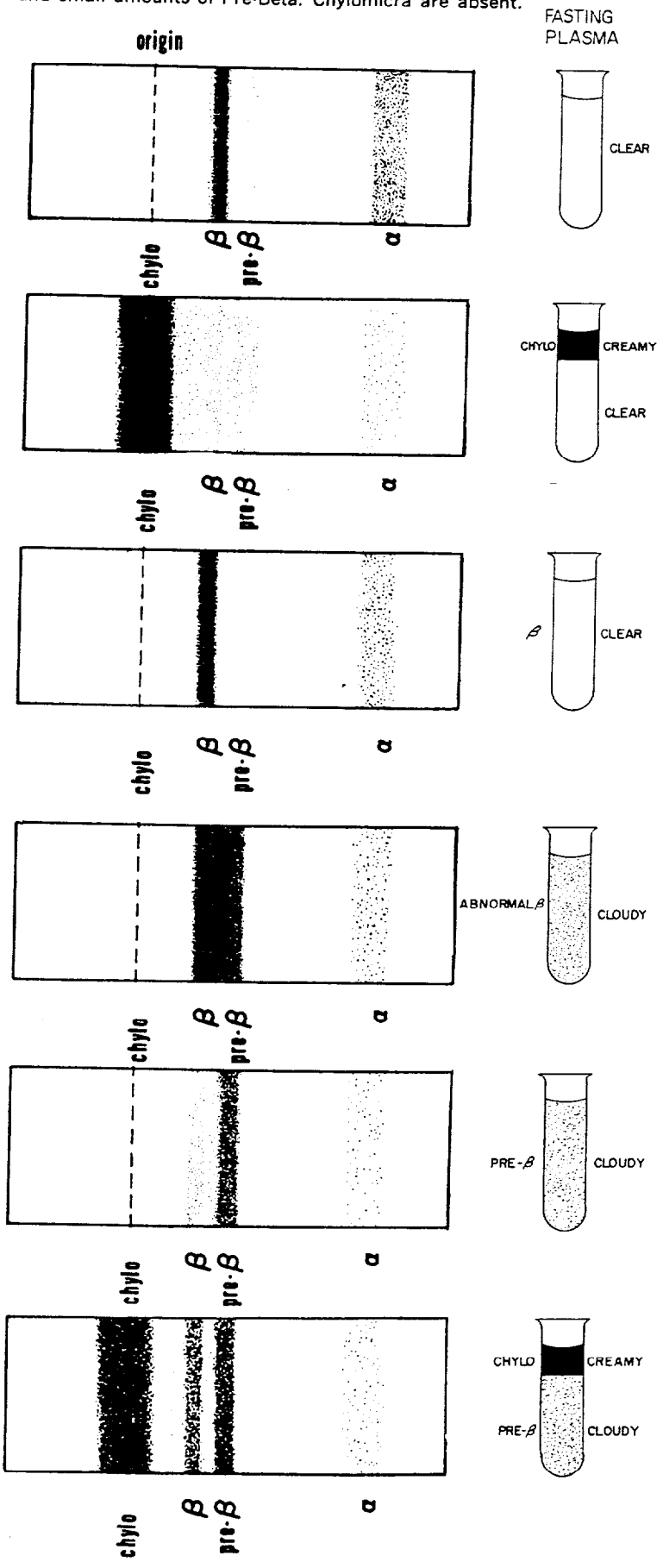


MECHANISMS OF HYPERLIPIDEMIAS

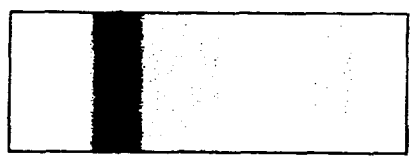


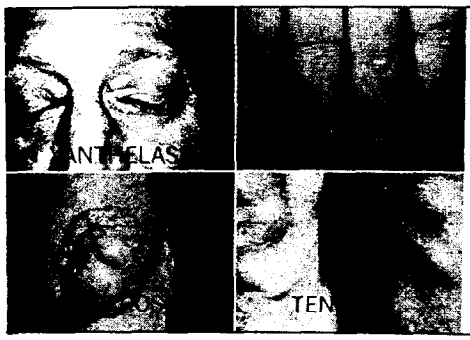
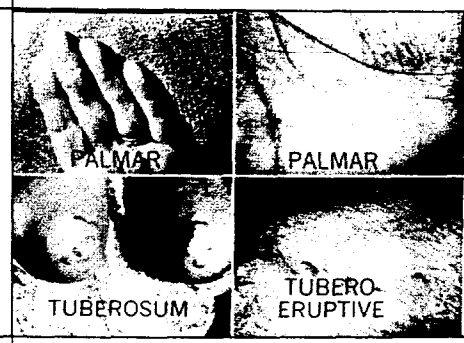
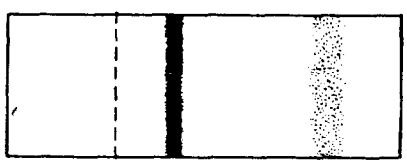
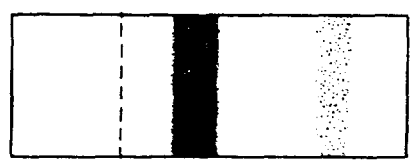
CLASSIFICATION OF HYPERLIPOPROTEINEMIAS

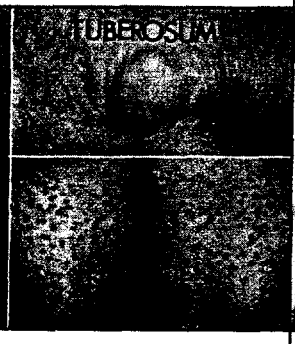
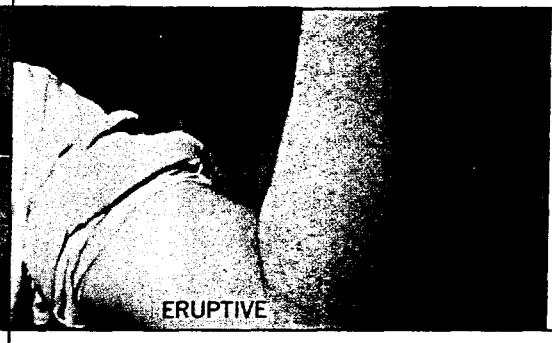
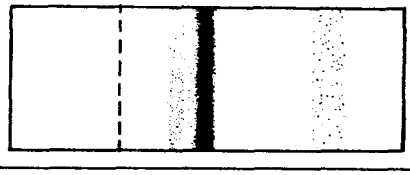
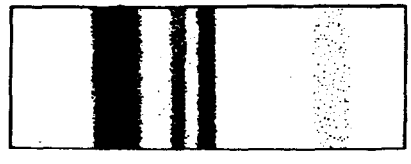
Electrophoresis of a normal fasting plasma reveals the following lipoproteins: Beta (≈ 85%), Alpha (≈ 15%), and small amounts of Pre-Beta. Chylomicra are absent.



TYPE I

SYNONYMS	BURGER-GRUTZ DISEASE
GENETICS	AUTOSOMAL RECESSIVE. RARE
XANTHOMAS	
CLINICAL MANIFESTATIONS	ONSET CHILDHOOD, HEPATOSPLENOMEGALY, ABDOMINAL PAIN, (PANCREATITIS?), LIPEMIA RETINALIS. CARDIOVASCULAR DISEASE: LOW
PLASMA LIPIDS	CHO: NORMAL OR SLIGHTLY INCREASED TRI: MARKEDLY INCREASED
GLUCOSE TOLERANCE	NORMAL
LIPOPROTEIN ELECTROPHORESIS	
MECHANISM	EXOGENOUS HYPERLIPIDEMIA. DECREASED ACTIVITY OF LIPOPROTEIN LIPASE
TREATMENT	LOW FAT DIET
SECONDARY FORMS	(A) SYSTEMIC LUPUS ERYTHEMATOSUS (B) LYMPHOMA

TYPE II	TYPE III
ESSENTIAL FAMILIAL HYPERCHOLESTEROLEMIA	IDIOPATHIC HYPERLIPIDEMIA
SIMPLE MENDELIAN DOMINANT. COMMON	RECESSIVE (?). LESS COMMON THAN II OR IV
	
ONSET CHILDHOOD OR ADULTHOOD. ARCUS CORNEA, ACCELERATED ATHEROSCLEROSIS	ONSET ADULTHOOD. HIGH INCIDENCE OF CARDIOVASCULAR DISEASE
CHO: MARKEDLY INCREASED TRI: NORMAL OR SLIGHTLY INCREASED	CHO: INCREASED TRI: INCREASED
USUALLY NORMAL	ABNORMAL
	
UNKNOWN. DERANGEMENT IN CHOLESTEROL METABOLISM	UNKNOWN. BETA LIPOPROTEINS WITH INCREASED CONTENT IN TRIGLYCERIDES. CARBOHYDRATE INDUCED
CLOFIBRATE. ESTROGENS. D-THYROXINE. NICOTINIC ACID. CHOLESTYRAMINE. DIET: REDUCE CHOLESTEROL INTAKE. POLYUNSATURATED FATS.	CLOFIBRATE AND LOW CARBOHYDRATE DIET. WEIGHT CONTROL
(1) LIVER DISEASE (2) NEPHROTIC SYNDROME (3) HYPOTHYROIDISM (4) MYELOMA (5) MACROGLOBULINEMIA	

TYPE IV	TYPE V
IDIOPATHIC HYPERLIPIDEMIA	DISEASE? SYNDROME?
SIMPLE MENDELIAN DOMINANT (?). MOST COMMON	PROBABLY GENETIC VARIANT OF TYPE IV (?). RARE
 	
ONSET ADULTHOOD, OBESITY FREQUENT, ABDOMINAL PAIN (PANCREATITIS?), CARDIOVASCULAR DISEASE.	ONSET EARLY ADULTHOOD, HEPATOSPLENOMEGALY, OBESITY, ABDOMINAL PAIN, LIPEMIA RETINALIS, CARDIOVASCULAR DISEASE NOT FREQUENT
CHO: NORMAL OR SLIGHTLY INCREASED TRI: MARKEDLY INCREASED	CHO: NORMAL OR SLIGHTLY INCREASED TRI: INCREASED
ABNORMAL	ABNORMAL
	
ENDOGENOUS HYPERLIPIDEMIA, MAY BE CARBOHYDRATE INDUCED	EXOGENOUS AND ENDOGENOUS HYPERLIPIDEMIA (MIXED FORM) LIPOPROTEIN LIPASE ACTIVITY MAY BE LOW
WEIGHT CONTROL, RESTRICTION OF CARBOHYDRATES, CLOFIBRATE, NICOTINIC ACID	WEIGHT CONTROL, DIET LOW IN FAT AND CARBOHYDRATES, CLOFIBRATE, PROGESTATIONAL HORMONES
(1) DIABETES MELLITUS (2) PANCREATITIS (3) GLYCOGEN STORAGE DISEASE (4) NEPHROTIC SYNDROME (5) PREGNANCY, GESTATIONAL HORMONES (6) MYELOMA (7) HYPOTHYROIDISM (8) PROGERIA (9) TOTAL LIPOATROPHY	DIABETES MELLITUS INSULIN DEPENDENT, PANCREATITIS ALCOHOLISM

References:

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3. Lees, R. S., and Hatch, F. T.: Sharper separation of lipoprotein species by paper electrophoresis in albumin-containing buffer, J. Lab. Clin. Med. **61:** 518 1963.
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